BIRTH DEFECT RISK FACTOR SERIES: CRANIOSYNOSTOSIS

DEFINITION

Trisomy 18 (Edwards syndrome) is the most common autosomal abnormality among live births after Down syndrome (trisomy 21). Most trisomy 18 cases result from total trisomy 18. A fraction of trisomy 18 cases result from mosaicism and translocation (Forrester and Merz, 1999; Carothers et al., 1999; Huether et al., 1996; Pradat, 1991; Buyse, 1990). Most trisomy 18 fetuses detected in mid-trimester do not survive to term (Hook et al., 1989).

Over the past several decades, women carrying a fetus with trisomy 18 have been found to have a prenatal marker screen with low maternal serum levels of alpha-fetoprotein, human chorionic gonadotropin, and estriol (Canick and Saller, 1993; Greenberg et al., 1992; Doran et al., 1986). Moreover, prenatal ultrasonography can detect a variety of structural anomalies frequently associated with trisomy 18 (Abramsky and Chapple, 1993; Vintzileos et al., 1987). Prenatal marker screening, ultrasonography, and definitive diagnosis by karyotyping through such procedures as amniocentesis and chorionic villus sampling, have allowed trisomy 18 to be identified in utero. Studies from various birth defects surveillance systems have found that, in regions where elective termination is allowed, prenatal diagnosis and elective termination reduce the prevalence of trisomy 18 (Chaabouni et al., 2001; De Vigan et al., 2001; Forrester and Merz, 1999; Carothers et al., 1999; Forrester et al., 1998; Abramsky and Chapple, 1993; Pradat, 1991).

ETIOLOGY

Trisomy 18 involving total trisomy 18 results from nondisjunction, usually in formation of the eggs or sperm, where one gamete ends up with an extra chromosome 18. Nondisjunction may occur in the first meiotic stage (MI) or the second meiotic stage (MII).

The extra chromosome 18 is of maternal origin in 90-97% of the cases and of paternal origin in 3-10 percent of the cases. Among trisomy 18 cases of maternal origin, 31-39% result from nondisjunction in MI and 61-69% result from nondisjunction in MII (Bugge et al., 1998; Nicolaidis and Petersen, 1998; Eggermann et al., 1996; Ramesh and Verma, 1996; Fisher et al., 1995; Jacobs and Hassold, 1995; Fisher et al., 1993; Ya-gang et al., 1993).

DEMOGRAPHIC AND REPRODUCTIVE FACTORS

Risk of trisomy 18 is well known to increase with increasing **maternal age** (Naguib et al., 1999; Baty et al., 1994; Buyse, 1990; Goldstein and Nielsen, 1988; Schreinemachers et al., 1982). Trisomy 18 risk has been associated with increasing **paternal age**; however, once maternal age is taken into consideration the association with paternal age tends to disappear (Naguib et al., 1999; Baty et al., 1994).

Race/ethnicity has not been reported to influence trisomy 18 risk (Buyse, 1990). One study found that, of the four racial/ethnic groups examined (white, Far East Asian, Pacific Islander, Filipino), trisomy 18 risk was highest for Far East Asians and lowest for Pacific Islanders (Forrester and Merz, 1999). However, the differences in risk appeared to be due to differences in maternal age distribution among the racial/ethnic groups. One study reported increased risk of Edward syndrome among offspring of Vietnamese mothers when compared with offspring of non-Hispanic white mothers in California (Shaw et al., 2002).

Geographic area may influence trisomy 18 risk. One investigation reported higher trisomy 18 rates among urban residents (Forrester and Merz, 1999). This increased risk remained after controlling for maternal age. Trisomy 18 prevalence can demonstrate **seasonal variation** (Naguib et al., 1999).

Several studies have reported a **secular trend** for trisomy 18, with the prevalence of the aneuploidy increasing over time. However, in one study this trend was believed to reflect improvements in ascertainment of the aneuploidy (Pradat, 1991). In the other study the increase in trisomy 18 prevalence over time was considered due to increasing numbers of births to older women and increasing prenatal diagnosis of affected pregnancies (Forrester and Merz, 1999). There does not appear to be **seasonal variation** in trisomy 18 rates (Videbech and Nielsen, 1984).

Infant sex influences the risk for trisomy 18. Females are more likely than males to have the aneuploidy (Forrester and Merz, 1999; Naguib et al., 1999; Carothers et al., 1999; Riley et al., 1998; Huether et al., 1996; Pradat, 1991; Buyse, 1990; Goldstein and Nielsen, 1988). One study found that sex ratio varied with race/ethnicity; however, this variation was attributed to small sample size (Huether et al., 1996). Trisomy 18 is also associated with lower **birth weight**, **prematurity**, and **intrauterine growth retardation** but not **plurality** (Rasmussen et al., 2001; Riley et al., 1998; Mili et al., 1991).

The **recurrence risk** for trisomy 18 has been reported to be approximately 1% (Baty et al., 1994; Buyse, 1990).

FACTORS IN LIFESTYLE OR ENVIRONMENT

No lifestyle or environmental factors have been definitively reported to affect trisomy 18 risk. However, the differences in trisomy 18 prevalence between populations (Forrester and Merz, 1999; Naguib et al., 1999) suggest that environmental factors may influence risk for the aneuploidy.

One study has reported that women who had infants or fetuses with trisomy 18 were more likely to have mutation in the **methylenetetrahydrofolate reductase (MTHFR) gene** but not the **methionine synthase reductase (MTRR) gene** (Hassold et al., 2001).

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Please Note: *The primary purpose of this report is to provide background necessary for conducting cluster investigations. It summarizes literature about risk factors associated with this defect. The strengths and limitations of each reference were not critically examined prior to inclusion in this report. Consumers and professionals using this information are advised to consult the references given for more in-depth information.*

This report is for information purposes only and is not intended to diagnose, cure, mitigate, treat, or prevent disease or other conditions and is not intended to provide a determination or assessment of the state of health. Individuals affected by this condition should consult their physician and when appropriate, seek genetic counseling.